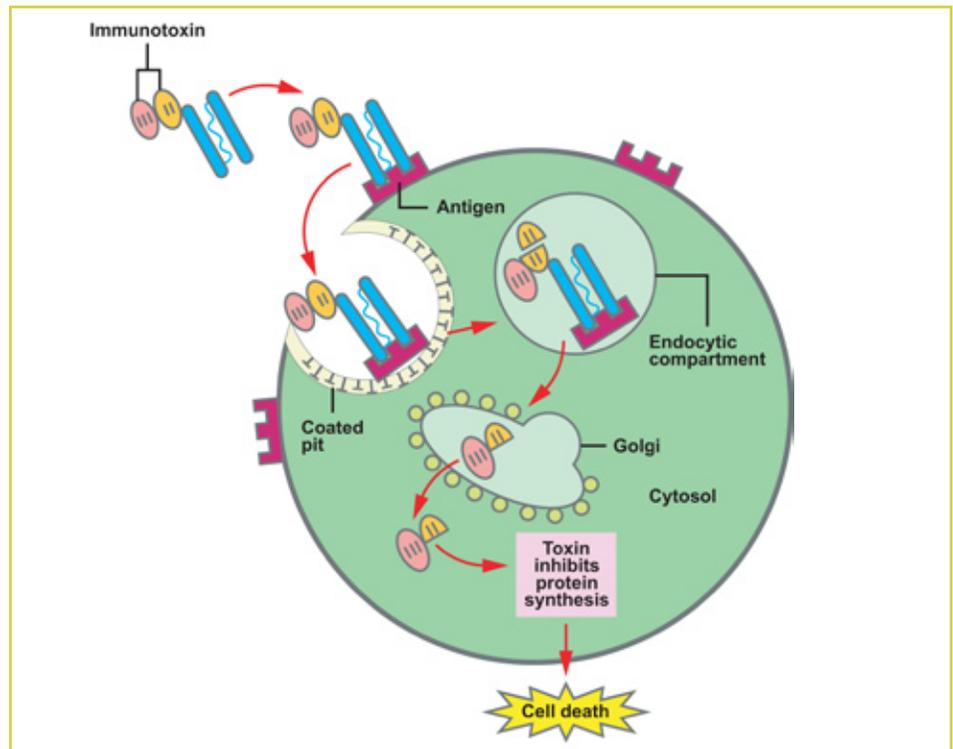


Designing Trojan Horses

Waging battle against cancer cells without inflicting damage on normal tissue has long been a goal for cancer treatment. A new type of drug called *immunotoxins* may help make this goal a reality.

Much like the Greeks used a wooden horse to get soldiers inside the gates of Troy, immunotoxins use clever genetic engineering to get a lethal toxin inside cancer cells. Each immunotoxin consists of two components—an antibody and a toxin—that are fused together. The custom-designed antibody acts as a homing signal, seeking out a specific target present on the surface of cancer cells. When the antibody binds its target, the whole immunotoxin is brought inside the cell. Unwittingly, the cancer cell has exposed itself to a powerful poison, a mistake that will likely condemn it to death.

The first step of making an effective immunotoxin is finding a good target. A CCR research team led by Ira Pastan, M.D., Chief of the Laboratory of Molecular Biology, has identified numerous targets with potential to facilitate toxin delivery to cancer cells while leaving most or all normal cells alone. A promising new target—FCRL1 (Fc receptor like 1)—is described in a paper authored by postdoctoral fellow Xing Du, Ph.D., and other Pastan lab members in the September 25, 2007, online edition of *Blood*.



A new immunotherapy is part antibody—two variable chains joined by a disulphide bond—and part immunotoxin. The antibody region binds to antigen on the cancer cell's surface and enters the cell through the coated pits. There the immunotoxin is cleaved into two fragments and translocates to the cytosol where it blocks protein synthesis and triggers cell death.

Pastan's group became interested in FCRL1, a cell surface receptor selectively expressed by B cells, when they learned that the protein is present at high levels in tumor cells of patients with chronic lymphocytic leukemia (CLL). Suspecting that it may be a good immunotoxin target, the Pastan lab created a series of antibodies able to interact with FCRL1 but not with other FCRL family members. They then constructed a pair of immunotoxins

by fusing portions of two of their new antibodies to a fragment of exotoxin A, a deadly protein made by the pathogenic *Pseudomonas* bacteria.

Tests in cultured cells showed that the Pastan immunotoxins are able to kill malignant cells that express FCRL1, providing further evidence that the protein may be useful as a therapeutic target. Two additional factors bode well for future use of at least one of

the immunotoxins in the clinic. First, its cytotoxic strength is comparable to that of immunotoxins that are showing promise in clinical trials. Second, it is stable at body temperature for at least 8 hours, which provides enough time for a drug administered to a patient to get to tumor cells.

Using their antibodies, the Pastan lab found that FCRL1 is frequently

present in other B-cell malignancies in addition to CLL, including follicular lymphomas, hairy cell leukemias, and mantle cell lymphomas. This discovery indicates that their new immunotoxins, or others like them, may be effective against a number of tumor types; however, future experiments in animal models and clinical trials will be necessary to determine whether these immunotoxins are capable of

delivering a death blow to tumor cells in patients.

Reference

Du X, Nagata S, Ise T, Stetler-Stevenson M, Pastan I. FCRL1 on chronic lymphocytic leukemia, hairy cell leukemia and B-cell non-Hodgkin's lymphoma as a target of immunotoxins. *Blood* Sep 25, 2007 [Epub ahead of print].